REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

New claim 35 has been added, corresponding to original claim 1, and includes a further limitation that the compound has no contraction activity of the urethra muscle. This is supported in the specification, for example, on page 8, line 10. New claim 36 is further added based upon claims 1, 2 and 11. The Ar moiety of the compound of clam 36 is not a phenyl group but a condensed ring. Thus, since the chemical structure of the compound of claim 36 is explicitly different from that of the cited compound, claim 36 is deemed to clearly define over the cited reference.

Claims 1-13 and 17 were rejected under 35 USC 112, second paragraph, as being indefinite. The basis of the rejection is that claims 1 and 17 recite the limitation of "non-carbamate amine compound". However, the rejection points out that when Y is an amino group of $-NR^4R^5$ wherein either R^4 or R^5 can be substituted "acyl group", the subject compound contradicts the term "non-carbamate amine compound" of the independent claims.

Generally, "carbamate" is a term used for the ester of carbamic acid, and does not include amide compounds. Also the structure of "carbamate" is defined in the present specification (e.g. page 2, line 8; page 96, line 20). That is, an amide structure is not included in the definition of "carbamate" of the present invention.

On the other hand, the substituent on Y of the present application includes an amino group of $-NR^4R^5$ wherein either R^4 and R^5 can be a substituted "acyl" group (page 41, line 8). An "acyl" group includes a group represented by the formula: $-(C=O)-OR^2$. This leads to a possibility of including a "carbamate" group in the present compounds.

Accordingly, the group represented by the formula: $-(C=O)-OR^2$ has been deleted from the definition of "acyl" in claim 9.

In view of the foregoing, this ground of rejection is deemed to be overcome.

Claim 17 was rejected under 35 USC 112, first paragraph, as lacking enablement. The basis of the rejection is that the specification does not reveal the proportion of an α-blocker and a non-carbamate amine compound to administer. The rejection is further based upon the position

that without guidance on what proportion of each agent to combine, mixing the two agents on administration could fatally decrease the blood pressure of the subject. The rejection further states that the state of the art does not yield any teaching for such a mixed composition. This ground of rejection is respectfully traversed.

The content of the non-carbamate amine compound having AChE inhibitory action and the dosage as a therapeutic agent for urination difficulty in a combined application are described on pages 108-109 of the specification.

In addition, the mixing ratio is determined based on an effective dose of each drug to be used in combination and taking into consideration the extent of *in vivo* activity and *in vitro* activity of each drug.

Combination therapy is well known in the art. The following two Japanese documents disclose a combination therapy in clinical study though they do not concretely disclose a combined application of AChE inhibitor and α-blocker.

(1) Katsumi T., Murayama K., Hinyokika Kiyo, 38, 1089-1092, 1992 "Clinical effects of distigmine bromide (Ubretid), a cholinesterase inhibitor, on micturition disturbance by benign prostatic hypertrophy---comparative study of distigmine bromide and the combination of distigmine bromide and adrenergic blocker".

(2) Yamanishi T., Yasuda K., Kamai T., Tsujii T., Sakakibara R., Uchiyama T., Yoshida K., Int. J. Urol., 11, 88-96, 2004.

"Combination of a cholinergic drug and an α-blocker is more effective than monotherapy for the treatment of voiding difficulty in patients with underactive detrusor".

Copies of these references are submitted concurrently herewith in an IDS.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.

An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance.

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Therefore, a skilled person can easily determine the mixing ratio in a combined application according to routine experimentation. In summary, the skilled person can make and use the claimed composition without undue experimentation, taking into consideration the teachings of the specification and the knowledge in the art.

Accordingly, it is believed that this ground of rejection is untenable and should be withdrawn.

Claims 1-3 and 6-9 were rejected under 35 USC 102 as anticipated by U.S. Patent No. 5,864,039. This ground of rejection is respectfully traversed.

The basis for the rejection is that the claims read on the treatment of dysuria which is disclosed in column 3 of the cited reference. The rejection is further based on the description of two compounds on lines 32 and 34 of column 18 of the cited patent as falling within the scope of the claims.

The cited reference describes the reference compounds used to treat "dysuria caused by urinary obstruction" in column 3, line 27. Dysuria is a painful or difficult urination.

The two compounds described in column 18, lines 32 and 34 of the cited reference are included in the compound of the present application.

However, the feature of the cited two reference compounds is a selective 5-HT4 agonist, and there is no description about AChE inhibitory action of these compounds. While the non-carbamate amine compounds having an AChE inhibitory action of the present application have an action of potentiating the contractive force of bladder muscle, but no contractive action of urethra muscle. Based on these findings, an unexpectedly high protective or therapeutic effect for urination difficulty of the compound of the present application was found out.

Therefore, the pharmacological action and effect of the compound of the present application are different from those of the compounds of the cited reference.

Thus, the cited reference fails to disclose or suggest a method for improving excretory potency of an urinary bladder. In view of the foregoing, it is respectfully submitted that the claims are not anticipated by the cited reference.

Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully solicited.

Lastly, claims 1-13 and 20 were rejected under 35 USC 103 as being unpatentable over the combined teachings of Goto et al. in view of Tobin et al. and Lai et al. This ground of rejection is respectfully traversed.

It may be easy for a skilled person to think of being able to promote the contraction of bladder muscle by inhibiting AChE based on the disclosure of cited references. Tobin et al. and Lai et al. describe that the contraction of bladder muscle is induced by AChE. However, being able to promote the contraction of bladder muscle does not directly lead to an action of improving excretion potency of bladder (treating effect of urinary disturbance). More specifically, AChE inhibitors such as distigmine promote the expected contraction of bladder muscle and yet at the same time contract the urethra muscle to raise the urethra resistance. As a result of these actions, the urinary efficiency is not improved. Furthermore, although U.S. 5,527,800 discloses that the non-carbamate compounds described in the present application have an AChE inhibitory action, there is no description or teaching about potentiating the contraction for bladder muscle.

The present invention is based on the findings that a non-carbamate amine compound having AChE inhibitory action has an excellent contraction activity for bladder muscle, but unexpectedly, has no contraction activity for urethra muscle and consequently, it has high urinary efficiency, and excellent action of improving excretion potency of bladder and treating effect for urinary disturbance.

Even if the cited documents are combined which have no description or teaching about contraction activity for bladder muscle and treating effect of urinary disturbance, the outstanding effects of the present invention cannot be suggested.

In view of the foregoing, it is believed that each ground of rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance. Accordingly, such allowance is solicited.

Respectfully submitted,

Yuji ISHIHARA et al.

By: _____
Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Applicants

WMC/ksh
Washington, D.C. 20006-1021
Telephone: 202-721-8200
Facsimile: 202-721-8250
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